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MEDLINE(R)

13203188 PMID: 11336243
Premenopausal status accelerates relapse in node positive breast cancer: hypothesis links angiogenesis, screening controversy.

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Breast cancer research and treatment (Netherlands) Feb 2001 , 65 (3) p217-24 , ISSN: 0167-6806--Print Journal Code: 8111104
Publishing Model Print; Comment in Breast Cancer Res Treat. 2001 Nov;70(2) 155-6; Comment in PMID 11768606; Comment in Breast Cancer Res Treat. 2002 Mar;72(2):185-6; author reply 186-7; Comment in PMID 12038709
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Much attention has been given to determining the benefit of mammographic screening to reduce breast cancer mortality. Eight randomized clinical trials have been conducted in four countries: the US, Canada, Scotland and Sweden. Trials report an early and stable 30% reduction in breast cancer mortality for women aged 50-59. For women under 50, unexpectedly, the early years of screening produce a disadvantage to the screened population. Only in later years does an advantage appear. To help understand this, we studied relapse patterns using a breast cancer database of 1,173 pre- and postmenopausal, node negative and positive patients treated with surgery only and having 16-20 years of follow-up. This approach is relevant since at least five of the eight screening trials began before the widespread use of adjuvant chemotherapy in the 1980s. Surgical cure rates were independent of menopausal status. However, a major difference in early relapse rate was found. In premenopausal and node positive patients, 27% of all distant relapses occurred within the first 10 months following resection. This is twice the early relapse frequency of any other clinical group. Using computer simulation, we interpret that these early relapses probably result from a disadvantage induced at surgery. A disinhibition or surgery/wounding induced angiogenic surge might be responsible. Disinhibition is known to occur in animal models such as Lewis lung where lung metastases are avascular and dormant until the primary is removed. Sudden outgrowth of tumor after wounding has been observed for a century. According to the simulation, in breast cancer this induction apparently accelerates inevitable relapses by a median of two years. This is offset in later years with a balancing reduction in relapses. These data suggest that the angiogenic switch may be upregulated more frequently among premenopausal women, perhaps depending upon the sex hormones. The acceleration would cause 0.11 deaths per 1,000 screened aged 40-49 subjects in years 2-3, a value comparable to the early year excess mortality in trials of a significant 0.15 deaths per 1,000 subjects. Equal screening advantage is predicted for node negative (but not node positive) pre- and postmenopausal patients. The acceleration of relapse after surgery may explain the paradoxical effect of mammographic screening for women under 50.